

CORRELATION BETWEEN SERUM VITAMIN D LEVELS AND SEVERITY OF SCHIZOPHRENIA PATIENTS IN THE DR. SOETOMO HOSPITAL

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ABSTRACT

Vitamin D deficiency is linked to various diseases such as kidney failure, liver damage, atherosclerosis, obesity, and psychiatric disorders such as depression and schizophrenia. This study aimed to analyze the correlation between serum vitamin D levels and schizophrenia severity. The subjects of this study were Schizophrenia patients who visited the Inpatient and Outpatient Clinic Department of Psychiatry of the Dr. Soetomo Hospital Surabaya. This research was a cross-sectional observational study, conducted in December 2017 - April 2018. The subjects consisted of 53 schizophrenia patients, vitamin D levels <30 ng/mL was found in patients (35 (66.04%); > 30 ng/mL (18 (33.96%)). Serum vitamin D levels tested by Enzyme-Linked Fluorescent Assay (ELFA) method using Vidas. The severity of schizophrenia was measured using a Positive and Negative Syndrome Scale (PANSS) score. Mean serum vitamin D levels in schizophrenia were 23.45 ± 9.16 ng/mL, mean serum vitamin D levels in males were 24.36 ± 9.80 ng/mL, and females 21.96 ± 7.98 ng/mL. The mean serum vitamin D level and PANSS scores of positive symptoms were 16.42 ± 8.50 . The mean serum vitamin D level and PANSS scores of negative symptoms were 15.60 ± 6.12 . The mean serum vitamin D level and PANSS scores of general psychopathology symptoms were 29.51 ± 10.29 . The statistical results showed no association between vitamin D levels and PANSS scores. This study indicated low serum vitamin D levels in schizophrenia. There was no association between serum vitamin D levels and the severity of schizophrenia using PANSS scores.

Key words: Vitamin D, schizophrenia, PANSS score

INTRODUCTION

Vitamin D is a steroid hormone, it is not only referred to as a vitamin, because vitamin D could be synthesized by skin exposed to Ultra Violet B (UVB) radiation. Vitamin D has two forms: ergocalciferol (vitamin D₂) found in fish and plants and cholecalciferol (vitamin D₃) synthesized in the skin from exposure to sunlight.¹ Previous studies suggested vitamin D had also been linked to mental illnesses including Alzheimer's disease, major depression, psychosis, and premenstrual mood disorder, so it was concluded that vitamin D had an important role in the central nervous system in the development and function of the normal nerves.²

Schizophrenia is a group of neuropsychiatric disorders characterized by symptoms such as hallucinations, delusions, confused thinking, and disorganization of speech.³ The early and chronic onset of the disease causes problems in patients and families. The relapse that occurs can show positive

symptoms such as delusions, suspicion, and hallucinations.⁴ Surveys have been carried out in various countries, and almost all show incidence rates per year of schizophrenia in adults within a quite narrow range between 0.1-0.4 per 1,000 populations.⁵ Prevalence of adults ranges between 1-17 people per 1,000 populations. The number of people with schizophrenia around the world can be estimated at 29 million, of whom 20 million live in developing countries.⁶ Schizophrenia is caused by a neurodevelopmental defect that disrupts early brain formation during specific but as yet unknown.⁷ Studies of rats with vitamin D deficiencies showed histologic and anatomic changes in brain development as a result of vitamin D deficiencies. In particular, studies showed a narrowing of the anterior and posterior cingulate and medial and occipital cortical areas.⁸ Vitamin D rich diets or vitamin D supplements have resulted in positive outcomes when added to treatment for some psychiatric illnesses like major depression,

Alzheimer's disease, and premenstrual dysphoric syndrome. A correlation between schizophrenia and low levels of vitamin D during the prenatal period and the early childhood have been well demonstrated. However, the influence of low vitamin D status on symptom severity in patients with schizophrenia has only recently begun to be investigated. Studies in the literature that compare vitamin D levels and disease severity have obtained varying results.^{9,10}

Geographical differences, different phases of the occurrence of disorders such as acute phase, chronic, acute exacerbations and remission, seasons of taking blood samples, history of psychoactive drugs use, age, sex, occupation, Body Mass Index (BMI) and sunlight exposure can affect vitamin D levels in the body. The primary management strategy for schizophrenia is the antipsychotic drug although this approach is less effective in overcoming the negative symptoms and the side effects of the drug can harm and weaken the patients.¹¹⁻¹³ Oxidative stress and immune responses occur in schizophrenia patients, so in some studies, it has been suggested that impaired physiologic mechanisms can be corrected with nutritional intervention. Nutrition approaches as an adjuvant and antipsychotic drugs are expected to be useful in the management of schizophrenia.¹⁴ This study aimed to analyze the association of serum vitamin D levels and the severity of schizophrenia using PANSS scores.

METHODS

This research was an observational analytical study with cross-sectional design by examining vitamin D levels in schizophrenia patients and measuring the severity of schizophrenia symptoms. The study conducted in December 2017-April 2018 in Inpatient and Outpatient Clinical Medical Psychiatric Dr. Soetomo Hospital Surabaya. The diagnosis of schizophrenia, according to the Classification Guidelines and Diagnostic of Mental Disorders III (PPDGJ III) was performed by a Psychiatry consultant. The Positive and Negative Syndrome Scale (PANSS) is one of the most common scales in clinical studies for measuring symptom severity in patients with schizophrenia, seven items are measuring positive symptoms, seven for negative symptoms and 16 items corresponding to general symptoms. The PANSS consists of 30 items measuring specific symptoms, each item ranging from 1 (absent) to 7 (extreme). Residents of psychiatry performed evaluation of PANSS score under the supervision of a psychiatry consultant.

Subjects of the study were schizophrenia patients who met the inclusion criteria aged 18-50 years, willing to participate following written informed consent sheet, signed by parent or guardian or person in charge, before following any procedure related to the studied.

The exclusion criteria were schizophrenia patients taking antiretroviral drugs, rifampicin, anti-epilepsy, or other drugs related to calcium, phosphate, and vitamin D metabolism. Schizophrenic patients with calcium or vitamin D supplements; Schizophrenia patients with liver disorders; Renal insufficiency; Parathyroid hormone disorders; Malabsorption syndrome; and Pregnancy listed in the medical record.

Vitamin D test was performed by Enzyme-Linked Fluorescent Assay (ELFA) method using VIDAS.¹⁵

Ethical clearance in this study was obtained from the Commission for Research Ethics at the Dr. Soetomo Hospital with: 732/Panke.KKE/XII/2017.

RESULTS AND DISCUSSION

This study comprised 53 patients with schizophrenia from the Inpatient and Outpatient Clinic Department of Psychiatry of the Dr. Soetomo Hospital Surabaya. Sociodemographic and clinical data were collected, including age, sex, education, employment status, marital status, and early age were diagnosed with schizophrenia, and serum vitamin D levels were shown in Table 1. Their range age was 18 years to 49 years, with an average of 34.23 ± 8.28 years. There were 33 males (62.3%).

The highest education was Senior High School (46.8%), 41 patients (77.4%) as unemployment. Most of the married status was unmarried 40 patients (75%). The mean age of initial diagnosis of schizophrenia was 25.42 ± 6.14 years, range 11-44 years. The initial age of diagnosis of schizophrenia for males in the range 10-25 years was 26 patients (78.8%).

The age peak of onset was 10 to 25 years for males and 25 to 35 years for females. This result may be because in females there is estrogen, a gonadal hormone that acts as a neuroprotective and a neurotransmitter that can regulate the dopaminergic system of the central nervous system, exert powerful effects in numerous regions of the brain, consequently affecting mood, cognition, and behaviour.^{16,17} In this study, the initial age of schizophrenia diagnosis in males range 10-25 years were 26 patients (78%) and females range 25-35 years were 17 patients (85%) (Table 1).

Table 1. Characteristics of study from 53 patients

Characteristics	Number
Age	
Mean ± SD	34.23± 8.29 years
Median	34.00 years
Range	18– 49 years
Sex N (%)	
Male	33 (62.3%)
Female	20 (37.7%)
Education, N (%)	
Junior High School	3 (5.7%)
Senior High School	46 (86.8%)
Scholar	4 (7.5%)
Occupation, N (%)	
Employment	12 (22.6%)
Unemployment	41 (77.4%)
Marital Status,N (%)	
Married	13 (24.5%)
Single	40 (75%)
Age at disease onset N (%)	
Male	
10-25 years	26 (78.8%)
26 -50 Years	7 (21.2%)
Female	
< 25years	2 (10%)
25 -35 years	17 (85%)
36 -50years	1 (5%)
PANSS scores	
Positive symptoms (mean±SD); (min-max)	16.42 ± 8.50; (7-37)
Negative symptoms(mean±SD); (min-max)	15.60 ± 6.12; (7-32)
General psychopathology (mean±SD); (min-max)	29.51 ± 10.29; (16-62)

The results in this study showed that serum vitamin D levels in schizophrenia subjects were 23.46±9.16 ng/mL, these results indicated that serum vitamin D levels were low in schizophrenia patients (Table 2). Previous studies had suggested that low prenatal vitamin D adversely affect brain development and had an increased risk of developing schizophrenia later in life.¹⁸

Table 2. Vitamin D levels of schizophrenia patients

Serum levels of vitamin D	
Mean	23.46 ng/mL
SD	9.16 ng/mL
Range	8.1 ng/mL – 44.5 ng/mL

These results indicated that serum vitamin D levels were low in schizophrenia patients (normal vitamin D levels = 30-100 ng/mL).

The finding of Vitamin D Receptors (VDR) in the central nervous system, in neurons and glial cells, further demonstrates the importance of vitamin D in early development to obtain optimal brain function.

Conversely, the absence of vitamin D in the embryonic brain results in increased levels of mitosis and decreased levels of apoptosis. Vitamin D plays a significant role in the cellular and transcriptional levels. Vitamin D is also involved in the rate of cell proliferation and cell death in the brain. Structure and proliferation due to vitamin D deficiency will be associated with abnormal neurochemistry and behavior in adulthood.^{18,11} Vitamin D deficiency is also influenced by several factors such as; genetic, ethnic, age, seasonal and geographic factors, dietary intake of vitamin D, sunlight exposure and low economic status.¹⁹

The results of this study showed that serum vitamin D level in males was 24.36±9.80 ng/mL and females was 21.96±7.98 ng/mL, there was no significant difference between serum vitamin D levels in males and females (p=0.393) (Table 3).

These results were consistent with the study of Cieslak *et al.* showing serum males vitamin D levels of 18.4±7.5 ng/mL and females 16.5±9.9 ng/mL.²⁰ Lally *et al.* obtained mean serum vitamin D levels in

males of 12.2±7 ng/mL and females 12.6±7.8 ng/mL.²¹ Indonesia, especially the city of Surabaya, is a tropical area close to the equator and has only two seasons, rainy and dry season.

The geographical location is flat and just a few meters above sea level, the temperate climate can reach 33°C, allowing each individual gets exposure to the sun. Pearce reported that sunlight exposure for 20 to 30 minutes on the face and forearms at midday was estimated to generate the equivalent of around 2,000 IU of vitamin D.²²

The result of Spearman correlation test between serum vitamin D level and PANSS scores of positive symptoms showed a significance value of 0.823 (p>0.005); r=0.032, meaning there was no significant correlation between serum vitamin D level and positive symptoms PANSS scores.

In this study serum, vitamin D levels were not correlated with positive symptoms of PANSS scores, mean positive symptoms PANSS scores in this study was (16.42±8.50) (Figure 1). This finding was following studies conducted by Itzhaky *et al.*, mean positive symptoms PANSS scores (19.6±11.8), there was no significant correlation between serum vitamin D levels and PANSS score of positive symptoms.¹² Likewise, with Lally *et al.* there was no significant correlation between vitamin D levels and

PANSS scores of positive symptoms (p=0.823).²¹ The results of the same study can be due to the research subjects taken mostly from the outpatient clinic, regardless of the duration of illness and episode of attack. The subjects of this study were schizophrenia patients who had received therapy, so had the same activities and lifestyle as healthy people and researchers did not consider the length of the subject suffering from schizophrenia.

The studies by Crews *et al.* reported there was a low serum vitamin D correlation with increased severity of positive symptoms.²³ Studies by Bulut *et al.* reported there was a correlation between low serum vitamin D levels with the severity of positive symptoms.¹¹ The subjects were schizophrenia patients who came with the first episode of psychotic attacks. Schizophrenia patients with a psychotic attack for the first episode have a habit of confining themselves so less exposed to sunlight, reduced activity, decreased appetite so did not get enough nutrition, especially vitamin D.

The result of Pearson correlation test between serum vitamin D level and PANSS score of negative symptoms showed a significant value 0.964 (p>0.005); r=0.006, there was no significant correlation between serum vitamin D level with negative symptoms PANSS scores.

Table 3. Serum vitamin D levels in males and females

	Mean	SD	Range	p
Male	24.36 ng/mL	9.80 ng/mL	8.1-44.5 ng/L	0.393
Female	21.96 ng/mL	7.98 ng/mL	10.3 – 35.9	

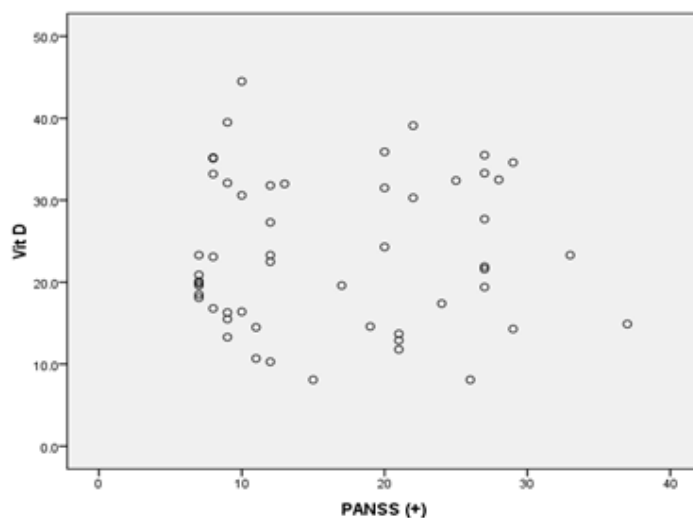


Figure 1. Serum vitamin D distribution with PANSS scores of positive symptoms

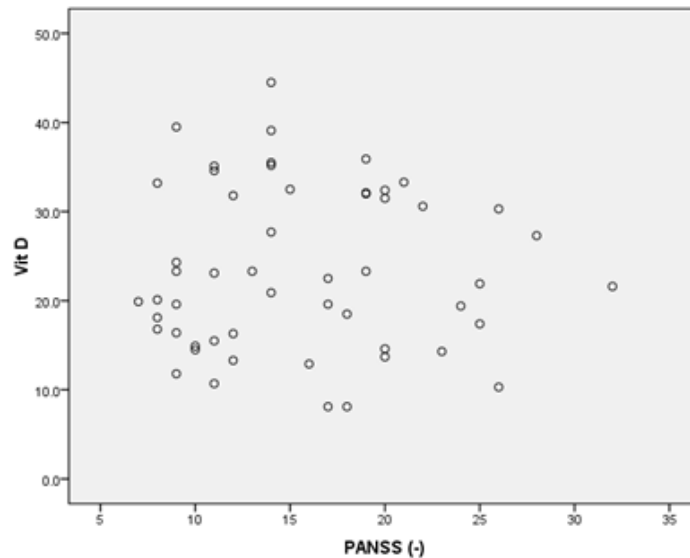


Figure 2. Serum vitamin D distribution with PANSS score of negative symptoms

The results of statistical analysis in this study showed no correlation between serum vitamin D levels and PANSS scores of negative symptoms ($p=0.964$) (Figure 2). This finding was following research of Itzhaky *et al.* there was no correlation between serum vitamin D levels and PANSS scores of negative symptoms ($p = 0.066$).¹² Haddad *et al.* reported that there was no significant difference between serum vitamin D levels and PANSS score of negative symptoms ($p=0.680$).²⁴ This result may be because, in this study, subjects were mature schizophrenia patients (18 years-50 years) the majority who visited the Outpatient Clinic, taking antipsychotic drugs, had activities and lifestyle such as healthy people.

On the other hand, a study by Graham reported there was an association between low vitamin D levels and the severity of negative symptoms. This difference might be because Graham's research subjects were adolescences with schizophrenia, who were still in the growing period, requiring more vitamin D intake for development.² The Cieslak study reported that there was a relationship between vitamin D levels and the severity of negative symptoms. The behavior of patients with negative symptoms was indicated by the presence of affective blunting, avolition/apathy, alogia, and disturbances of attention, leading to more deficient nutrition and less time spent outdoors that would contribute to lower vitamin D levels.²⁰

Previous studies suggested that vitamin D involved in the pathogenesis of specific symptoms in schizophrenia. Wrzosek reported that vitamin D was neuroprotective through the prevention of oxidative

stress in the central nervous system, and showed that oxidative stress caused negative symptoms through an imbalance in the excitative-inhibitory glutamate-GABA responses.^{25,26} Other studies have suggested that the decrease in glutamate (GLU) due to a dopamine deficit in the prefrontal cortex might lead to abnormalities of brain function associated with schizophrenia. A persistent defect in GLU transmission involving N-methyl D aspartate receptors (NMDA) was induced by dopamine dysfunction. Decreased dopamine activity might aggravate the negative symptoms and impaired neurophysiological function.²⁷

The result of Pearson correlation test between serum vitamin D level and PANSS scores of general symptom was showed a significant value 0.968 ($p>0.005$; $r=0.006$, meaning there was no significant correlation between serum vitamin D level with general psychopathology PANSS scores. Serum vitamin D levels did not correlate with PANSS score of general psychopathology symptoms ($p=0.968$), according to the study Itzhaky *et al.*, there was no correlation between serum vitamin D levels and PANSS scores.¹² Haddad *et al.* reported there was no correlation between serum vitamin D levels and PANSS scores of general psychopathology symptoms ($p=0.442$).²⁴ This finding could be due to the subjects of this study were obtained manly from the Outpatient Clinic (patients with mild disease symptoms) and had received treatment, whereas the previous studies recruited patients from hospitalization, which caused low levels of vitamin D, where patients have limited activity, so less exposed to sunlight (Figure 3).

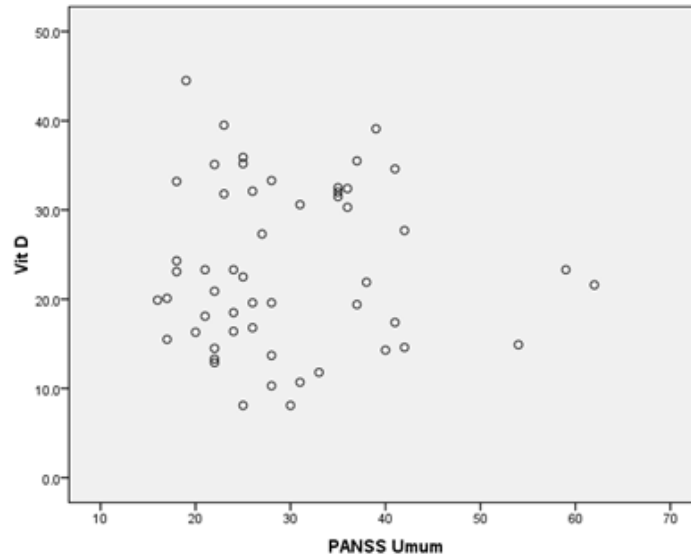


Figure 3. Serum vitamin D distribution with a PANSS score of general psychopathology symptoms

Different studies had reported by Yuksel, there was a correlation between vitamin D levels with PANSS score of general psychopathology symptoms. This difference was due to the grouping of the subjects between the remission and hospitalized patients. The hospitalized patients, there was a severe vitamin D deficiency and a high severity score compared with patients who had received treatment or remission.¹³

CONCLUSION AND SUGGESTION

There was no correlation between serum vitamin D levels, and PANSS score of positive symptoms, PANSS score of negative symptoms, and PANSS score of general psychopathology symptoms. This study was the first study to analyze the correlation between serum vitamin D levels and schizophrenia severity. This research was an observational analytical study with a cross-sectional design. Further research is needed to look for various factors affecting serum vitamin D levels and severity of schizophrenia patients, and investigate the association with longer follow up.

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